



Controversies in the Management of Metabolic Risks

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Cardiometabolic Risks [CMRs] such as hypertension, excess weight, obesity, type-2 diabetes and cardiovascular disease [CVD], have reached epidemic proportions worldwide [1-17]. In 2015, according to reliable estimates, more than 900 million adults had systolic blood pressure [SBP] of 140mm Hg or higher [1]. The global obesity epidemic may further increase SBP in some populations [2,4]. Since 1980, obesity has doubled in more than 70 countries [5]. The rising pandemic of obesity in many countries, has received major attention from public health and global health organization, yet not much has been done in terms of arresting, or reducing, the increase in the incidence of excess weight and obesity at the population level [6-8]. According to the experts, today's food environments exploit people's biological, psychological, social, and economic vulnerabilities, making it easier for them to eat unhealthy foods [6]. Regulatory actions from governments and increased efforts from food industry and civil society, will be necessary to break these vicious cycles [6-8]. In spite of the fact, that there is worldwide recognition of the rapid increase in the incidence of type-2 diabetes, the future economic consequences of the disease remain uncertain. It is estimated that global economic burden, will increase from US 1.3 trillion to 2.2 trillion [9]. Diabetes mellitus is considered number one killer, among all chronic metabolic diseases [13]. During the last fifteen years, the prevalence of type 2 diabetes has increased by fivefold worldwide [14]. During the same period in China, diabetes has increased by seventeen-fold [15]. According to Chinese researchers, the potential risk factors which could have contributed to the increasing prevalence and incidence of diabetes and impaired glucose tolerance in the Chinese population include, social economic development, urbanization, dietary pattern, and Westernized lifestyle. Hypertension, excess weight, obesity, metabolic syndrome, and diabetes are the driving force for increased incidence of acute vascular events, such as heart attacks and stroke [15-17].

In view of the fact, that all the known metabolic diseases were rapidly increasing, we at the University of Minnesota, started a Professional Society in 1993 [South Asian Society on Atherosclerosis and Thrombosis [SASAT], to create awareness and develop novel prevention strategies [18]. Looking back now, it looks like that there are more controversies reported, than standard guidelines, guidance statements or recommendations. For over four decades, various regulatory agencies as well as professional societies and Global Health Organizations, recommended consumption of low-fat or no-fat dairy products and consumption of no more than 3 eggs per week, to prevent excess dietary cholesterol. These recommendations were based on the results of long-term epidemiological studies in seven countries. Professor Ancel Keys of the University of Minnesota developed a 'diet-heart' hypothesis, based on his epidemiological experience. This was not really a new idea. This hypothesis has been controversial for nearly 100 years. The 'Lipid hypothesis', refers to the hypothesis, that serum cholesterol causes heart disease. Whereas, diet-heart hypothesis, refers to the hypothesis, that dietary saturated fat raises cholesterol and therefore raises heart disease. Frank Hu and Walter Willett, well-known epidemiologists from Harvard University, say that interest should not focus solely on serum cholesterol or low-density lipoprotein cholesterol [LDL-C], because the effects of diet on CVD can be mediated through multiple biological pathways [19].

The debate on whether dairy and dairy-derived fats are good or bad for health has been going on for decades. However, recent data from Cambridge, UK, seem to suggest that milk, cheese, and yogurt may be more beneficial than harmful. A new international study corroborates evidence, that dairy fats may lower risk of diabetes. Professor Mozaffarian says, "While dairy fats are recommended as part of a healthy diet, the U.S. and International guidelines generally recommend low-fat or non-fat dairy due to concerns about

adverse effects of higher calories or saturated fat,” Professor Darius Mozaffarian, senior author of this multi-country study also believes, that the current guidelines may call for a revision of dietary guidelines, that encourages people to avoid full-fat dairy. In a recent study, Chinese investigators have reported, that consumption of one egg per day, reduced CVD, ischemic heart disease, and major coronary events [21]. Under the Medical News and Perspectives, JAMA [December 5, 2018] published a report titled. “Whole-fat or Nonfat Dairy? Debate continues.” In this article, the authors report that a higher intake of total dairy, defined as more than 2 servings a day, was associated with a lower risk of death or a major cardiovascular event than no intake.

Freeman and associates have recently published a clinician’s guide for trending cardiovascular nutrition. According to these guidelines, clinicians should remember following key points:

1. Evidence supports the use of a diet high in fruits, vegetables, whole grains, and legumes.
2. Evidence for or against dairy products is limited by study design, potential biases of industry sponsored trials, and heterogeneity of dairy products.
3. Evidence demonstrates CVD risk associated with added sugars, including promotion of atherogenesis.
4. Limited evidence supports the avoidance of energy drinks, due to increased risk for arrhythmias, coronary spasm, and potential death. Readers are urged to refer to the part 1 and Part 11 of these guidelines, to understand the current con these guidelines, to troversies, related to cardiovascular nutrition [23,26].

In view of these controversies, Griffin and associates conducted a survey of General Practitioners [GP], to find out their understanding of these recommendations. They concluded that, “Although the GP response was poor, responders do seem to see dietary advice as part of their role, but do not consider themselves as experts. Education in this area should have a higher priority” [27]. In a consensus statement on dietary fats, Spanish researchers conclude, “replacing saturated fatty acids for monosaturated fatty acids and polyunsaturated fatty acids, reduces cardiovascular risk. Low-fat, high-carb diets appear to lack cardiovascular preventive effects, while high-fat, high-vegetable fat dietary patterns such as the Mediterranean diet, are protective, a reason why no upper limit on fat intake is established for the Spanish population” [28].

Now that we have discussed some of the dietary controversies related to the management of CVD risk, let us see what seems to be the key controversial CMR management issues, according to the re-

puted New England Journal for the year 2018. Of the 10 Top Cardiology Stories selected for the year 2018, majority of them were focused on prevention strategies [29]. The editorial team picked up the results of REDUCE-IT trial as the top story, in which researchers found that icosapent ethyl reduced cardiovascular risk beyond statins in patients with established CVD or diabetes. Despite the controversy about the unclear mechanism of action of this drug, editors thought that this was the preferred drug of choice. In contrast in the CIRT trial, methotrexate failed to reduce the risk, perhaps because the drug surprisingly, did not appear to affect inflammation, as measured by interleukin-1 β , interleukin-6 and C-reactive protein. The editors concluded that in the end, the inflammation hypothesis of atherosclerosis remains unproven. Contrary to this conclusion by the editors of NEJM, Ridker and associates, from Harvard University, have reported in NEJM of 2017, a study on the antiinflammatory therapy with Canakinumab, a monoclonal antibody for atherosclerosis disease [30]. In the discussion, the authors mention that CANTOS trial was designed to test directly, the inflammatory hypothesis of atherothrombosis.

During the European Society of Cardiology Congress in Munich, Germany, Professor Ridker, the Director, of the Center for Cardiovascular Disease Prevention, Harvard Medical School and Eugene Braunwald Professor of Medicine at Brigham and Women’s Hospital, Boston, Mass., said, “CANTOS demonstrates that targeting the IL-1- β -to-IL-6 pathway of innate immunity with Canakinumab reduces cardiovascular event rates. CANTOS trial thus provides critical proof-of-concept that inflammation inhibition, in the absence of lipid lowering or blood pressure reduction, can improve atherothrombotic outcomes.” In the same issue of NEJM, Watson has a review of Ridker’s studies [Ridker, *et al.* NEJM Nov 10, 2018], in which this group conducted additional studies on low dose methotrexate. They found that low dose methotrexate did not reduce atherosclerotic events, but it also did not reduce markers of inflammation, so it neither confirms nor refutes the inflammatory hypothesis of atherothrombosis. These results demonstrate, how the clinical trials could be misleading and generate controversies, if they are not conducted properly. However, we would like to inform the readers, that FDA has declined to approve Canakinumab [Ilaris] for cardiovascular risk reduction on the strength of data from CANTOS trial, adding another controversy to the debate about the role of inflammation in CVD events.

Another controversial topic discussed along with the Top Ten Stories is about the Aspirin. The utility of aspirin for the primary prevention of cardiovascular disease in patients with diabetes is not known. Diabetes confers cardiovascular risk for many indi-

viduals, and aspirin has the potential to reduce that risk, but some speculate that diabetes may reduce the antiplatelet effects of aspirin. Of course, there is no real proof or evidence for such speculations. We and other have reported in our earlier studies, that diabetes subjects have hyper active platelets, as well as a prothrombotic state. The data from ASCEND trial [NEJM Cardiology 2018] with randomized 15,480 subjects did demonstrate, that during a mean follow-up of 7.4 years, the incidence of serious vascular events was significantly lower in the aspirin group, than in the placebo group. As expected, the researchers observed gastrointestinal bleeding also in some participants. The comment on the outcome of this trial reported that, "The decision about whether these people would take aspirin depends on how they weigh these respective outcomes- and their absolute risk for these outcomes, using any of the traditional risk prediction tools. One other test that we suggest is to monitor urinary metabolites of thromboxane to assess the "at risk" patients, so that, those found at risk, could be provided additional prophylaxis. To add a personal note, we at the University of Minnesota recommended low dose enteric coated aspirin for diabetic subjects twice daily.

In the same series on Top 10 Cardiology Stories, Rodriguez reviews the studies on Triglyceride lowering and its benefit on CVD outcomes. REDUCE-IT is an international, industry sponsored study in which, icosapent ethyl [a highly purified Eicosapentaenoic acid ethyl ester] was evaluated in patients with established CV disease or diabetes, for its effect on triglyceride lowering. According to the researchers, during a 5-year follow up, compared with placebo, there was a 25% relative risk reduction and 5% absolute risk difference. Unlike other triglyceride lowering agents [niacin, fibrates and other omega 3-fatty acids], that have failed to show CV benefits, high dose icosapent ethyl appears to have impressive efficacy. These results confirm, that the mechanism of lipid lowering matters cannot be generalized, even among similar agents. More studies are needed to determine, if the observed benefits extend to other omega-3 fatty acids. A word of caution. In the April issue of JAMA [2018], in its News and Perspectives, the authors have reported recent findings on fish oil supplements as, "Another Nail in the Coffin for Fish Oil Supplements." The article concluded that fish oil capsules do little to protect patients with heart disease [31,32]. Having said that, I would like to remind the readers that in the REDUCE-IT studies, according to the researchers, a highly purified Eicosapentaenoic acid was used and not just any fish oil.

Metabolic alterations leading to metabolic risks, can develop at any time in the life of an individual. As we have articulated before, even intrauterine growth alterations could lead to the changes in the developing fetus, and lead to the "Fetal Origin of Adult Diseases [FOAD]." We have discussed these issues in our earlier publications [33]. Early metabolic risks include, excess sugar and fats in the circulating blood, oxidative stress, inflammation, endothelial dysfunction, hardening of the arteries, subclinical atherosclerosis, and development of atherothrombotic events. In view of these observations, it is important to develop novel approaches to the management of these early metabolic risks. Harvard researchers have indeed demonstrated, that maternal multiple micronutrient supplementation, offers beneficial effects on pregnancy outcomes in developing countries [34]. Several other studies also have shown, that multiple micronutrient supplementation for pregnant women, reduces low birth weight and has been recommended in low- and middle- income countries [35]. In the area of oxidative stress, it is possible to develop complementary therapies using Protandim [a mixture of five phytochemicals; Ashwagandha, Indian Green Tea, China Milk Thistle and China Turmeric] an herbal product promoted by the US researchers [36-38]. The transcription factor Nrf2 [nuclear factor erythroid-2-related factor-2, Nrf-2] for instance, a master regulator of detoxification, anti-oxidant, anti-inflammatory and other cytoprotective mechanisms, is raised by health promoting factors. This transcription factor activates the transcription of over 500 genes [so called survival genes] in the human genome, most of which have cytoprotective functions. The most healthful diets such as Mediterranean and Okinawa, are rich in Nrf2 raising nutrients. Modern diets are deficient in such nutrients. Studies by Joe McCord and associates on the effect of Protandim on various pathways have shown, significant modulation by this product not only of pathways involving antioxidant enzymes, but also those related to cardiovascular disease [38].

If you just Google the title of this article, you will get several references regarding Metabolic Syndrome. However, in this short commentary, we are discussing metabolic risks in the broadest sense, which will promote and facilitate the development of metabolic diseases, that contribute collectively to the precipitation of acute events associated with vascular diseases [heart attacks and stroke]. We have briefly discussed the controversies surrounding various interventions, including dietary modulation of carbohydrate, protein and lipid intake, fish oil supplementation, and many other therapeutic approaches. After reviewing the various topics, what stands out as reliable proof is the fact, that robust manage-

ment of modifiable risks as suggested in the INTERHEART studies, will reduce significantly the premature mortality related to CVD events [39]. It is important to realize that preventing premature mortality will not reduce, reverse, or prevent the global epidemic of "Metabolic Diseases." In view of this fact, various stakeholders, should develop immediate action plans, to address the issues related to this important public health problem [40-46]. Current food environments, exploit people's biological, psychological, social, and economic vulnerabilities, making it easier for them to eat unhealthy foods. In spite of these observations by the experts, it is hard to change the eating habits and lifestyle at the population levels. Creating awareness and educating all the stakeholders including, children, young adults, and women seems to be the only wise choice available at the time of this writing, for the prevention of chronic metabolic diseases.

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